Crystal Habit Changes and Dosage Form Performance

A. K. Tiwary
Punjabi University, Patiala, India

INTRODUCTION

A crystalline particle is characterized by definite external and internal structures. Habit describes the external shape of a crystal, whereas polymorphic state refers to the definite arrangement of molecules inside the crystal lattice. Crystallization is invariably employed as the final step for purification of a solid. Use of different solvents and processing conditions may alter the habit of recrystallized particles, besides modifying the polymorphic state of the solid. Subtle changes in crystal habit at this stage can lead to significant variation in raw material characteristics. Furthermore, various indices of dosage form performance such as particle orientation, flowability, packing, compaction, suspension stability, and dissolution can be altered even in the absence of significantly altered polymorphic state. These effects are a result of the physical effect of different crystal habits. In addition, changes in crystal habit accompanied with or without polymorphic transformation during processing or storage can lead to serious implications of physical stability in dosage forms. Therefore to minimize variations in raw material characteristics, to ensure reproducibility of results during preformulation, and to correctly judge the cause of instability and poor performance of a dosage form, it is essential to recognize the importance of changes in crystal surface appearance and habit of pharmaceutical powders. Fig. 1 depicts an overview of the critical stages where changes in crystal habit are likely to appear during pharmaceutical processing.

CRYSTAL HABIT CHANGES

The internal structure or polymorphic state represents the molecular arrangement within a crystal and is manifested in the form of a definite heat of fusion (ΔH_f) value. External structure or crystal habit is the outer description of a crystal and is described by its length, width, thickness, and surface appearance (roughness, smoothness, and porosity). Crystal growth may be impeded by adjacent crystals growing simultaneously or contacting container walls. As a result, the development of plane faces may be inhibited, leading to the formation of a tabular (moderate development of parallel faces), platy (excessive development of parallel faces), prismatic, acicular (inhibited width), or bladed (flattened acicular) crystal habit.[1,2]

Thus a single internal structure of a compound can have several different habits. In the case of delayed crystallization, an irregularly shaped crystal may be produced because it is constrained to occupy only the spaces left between already crystallized particles. Such irregularly shaped crystals are described as anhedral or allotriomorphic, and those bound by plane faces are known as euhedral or idiomorphic. However, anhedral crystals do have a regular arrangement of building blocks in the crystal lattice.

Crystallization of a solid may be influenced by formulation and process variables of the crystallization process. However, it is difficult to delineate the role of a process variable on crystal habit because an alteration of the variable often leads to change in both deposition and dissolution rate of the material during the crystal growth phase. In addition, the processes are interactive and not independent of each other. For example, a change in temperature simultaneously alters the viscosity of crystallization solvent as well as saturation level of the solute. Hence an increase in temperature affects both deposition and dissolution rate of the solute on crystal nuclei. Similarly, rate of stirring influences the onset of nuclei formation because of its effect on the temperature of the solution. It also influences the growth of crystals because of the uniform distribution of solute throughout the solution. The net result of an altered variable is usually dependent on more dominant factors such as initial supersaturation level, nature of the co-solvent, crystallizing solvent, cooling rate, etc. Few important factors that alter crystal habit and the anticipated influence of altered habit on dosage form performance are summarized in Table 1.

Changes in polymorphic state as a result of the employment of different crystallization conditions and the influence of these polymorphic states on stability and biological attributes of dosage forms have been receiving focused attention of many researchers. However, not much importance seems to have been given toward crystal habit perhaps because of the complexity of the crystallization process and its ability to simultaneously modify

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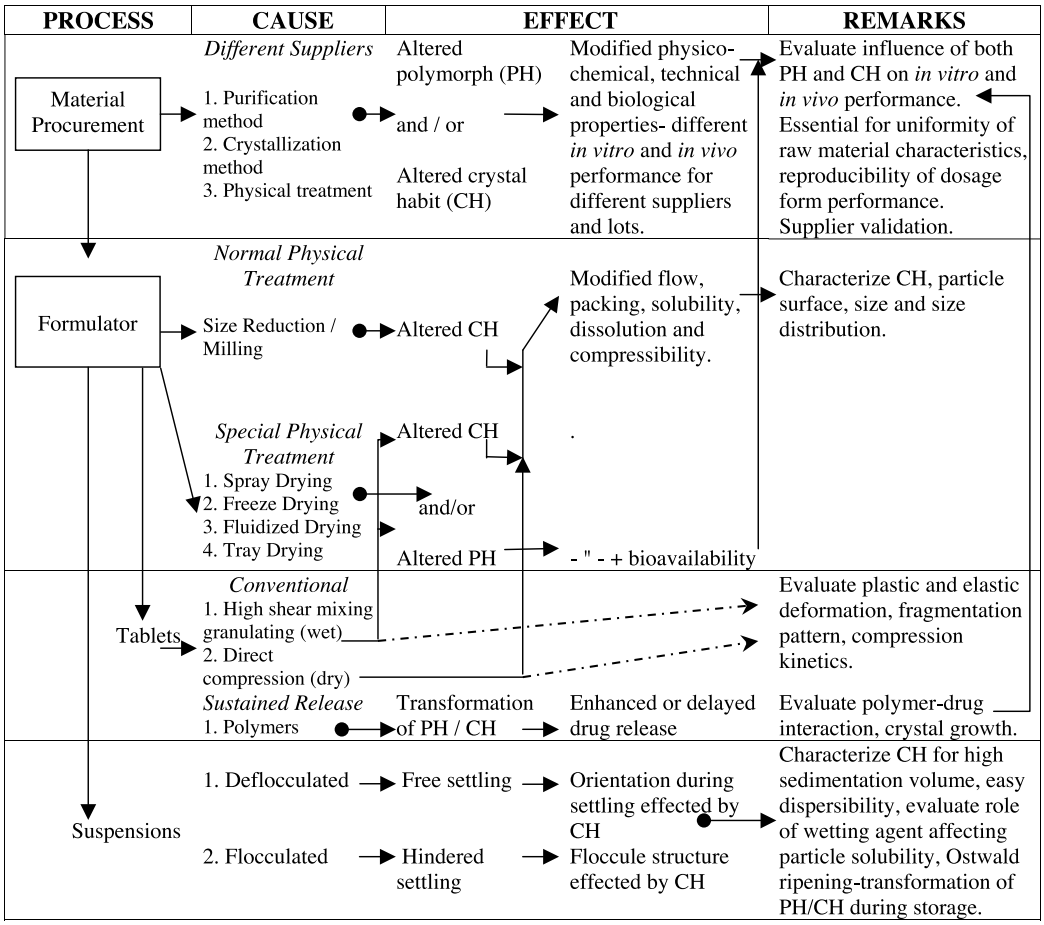

Fig. 1 Flow chart of the cause and effect relationship outlining the importance of crystal habit in dosage form design and performance.

both habit and polymorphic state of compounds. Nevertheless, because of the great impact of this seemingly trivial crystal property on dosage form performance, there is a need to study the important factors that influence crystal habit.

FACTORS INFLUENCING CRYSTAL HABIT

Degree of Supersaturation

The degree of supersaturation of the mother liquor or difference in concentration of solute on opposite sides of a growing crystal influences crystal habit. The effect of supersaturation on the change in habit was described by an equation, $y/x = k\Delta G^n$, where y/x is the ratio of crystal length to breadth, k is a coefficient of proportionality depending on diffusion, ΔG is the degree of supersaturation (moles/1000 mol of solvent at the moment of nuclei formation), and n is a number that depends on the crystallographic classification and the chemical composition of the substance.[3]

Barium sulfate precipitation has been reported to be controlled initially by nucleation reaction and, finally, by growth reaction. The growth kinetics was represented by the equation:

$$\frac{da}{dt} = -k(C_o - C)^{2/3} a^q$$

where a is the mean ionic activity of Ba^{2+} and SO_4^{-2}, t is the time, C_o and C are the molar concentrations of barium sulfate available at t_o and t, respectively, k incorporates the kinetic constant and the shape factor, and q is proportional to the rate of change of the mean ionic activity and surface of the particle.[4]

However, Nielsen[5–7] reported the growth of barium sulfate to be controlled by a chemical reaction in which

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Table 1 Influence of process variables of crystallization on crystal habit and dosage form performance

Process variable of crystallization	Possible influence on crystal habit	Possible influence on crystal/dosage form performance[a]
Supersaturation		
1. More saturation or significant solute–solvent interaction	Rate of nuclei formation is greater than crystal growth	Fine particles are produced
	More growth in one direction producing needle-shaped crystals	Needle-shaped crystals exhibit poor flowability and cause bridging in hopper
2. Less saturation or insignificant solute–solvent interaction	Platy crystals are produced	Platy crystals exhibit greater dissolution, but are not preferred for tablet dosage form
Rate of cooling and degree of solution agitation		
1. Rapid cooling	Rapid crystal growth occurs and asymmetric (thin platy crystals) are produced	Platy crystals are not preferred for tablet dosage forms
2. Slow cooling	Rate of crystal growth decreases, and symmetric crystals are produced	Using symmetric, compact crystals gives more predictable and consistent performance
3. High speed of agitation	Even distribution of crystallizing solute on the nuclei produces elongated crystals with small particle size distribution	Desirable particle size range can be obtained; such crystals exhibit good flowability and less sedimentation in suspensions
4. Low speed of agitation or unstirred solutions	Crystallizing molecules deposit on selected crystal face, producing large platy crystals	Crystals with large particle size are unsuitable for formulations
Nature of crystallizing solvent		
1. More affinity for crystallizing solute	Formation of nuclei is delayed and fine, symmetric crystals are produced	Desired crystal size with better dissolution and flowability
	Interaction of certain functional groups between solvent and solute may impede growth at selected crystal faces	Elongated crystals may be produced that are suitable for formulations because of their better flowability and sedimentation behavior
	Requires a high ratio of crystallizing solute/crystallizing solvent for producing well-defined shaped crystals	
2. Less affinity for crystallizing solute	Nuclei are formed immediately and crystal growth is rapid; relatively larger crystals are produced	
	A low ratio of crystallizing solute/crystallizing solvent is required for obtaining well-defined shaped crystals	
Temperature of crystallizing solvent		
1. Low temperature	Rapid nuclei formation because of spontaneous decrease in saturation level produces irregular shaped crystals	Irregular (dendritic) shaped crystals are not suitable for tableting
2. High temperature	Nuclei formation is delayed and fine, symmetric crystals are produced	Desirable shape and size of crystals can be obtained that are suitable for dosage forms
Presence of impurities		
1. Adsorbable ions, solute molecules	Inhibition or excessive growth of certain crystal faces	Desirable crystal morphology can be obtained during purification by recrystallization
2. Structural compatibility between polymer and drug	Interaction of functional groups between polymer and crystallizing solute restricts growth at certain crystal faces	Prevention of habit transformation

[a]No generalization can be made with regard to influence of process variables of crystallization on crystal habit and dosage form performance because the influence of a process variable is interactive and not independent of the other variable. The influences listed here should be used as a guideline only. (From Ref. [72], p. 701, by courtesy of Marcel Dekker, Inc.)

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the crystal formation was a fourth-power step. The precipitation was found to be diffusion-controlled when the concentration was greater than 0.4 mM and could be characterized by the equation:

$$K_o t = \int_0^a a^{-1\,3}(1-a)^{-1}\mathrm{d}a$$

When the concentration was less than 0.4 mM, the kinetics could be described by the equation:

$$K_R t = \int_0^a a^{-2\,3}(1-a)^{-4}\mathrm{d}a$$

where a represents the degree of precipitation. Hence an initial concentration less than 0.5 mM produced small prismatic crystals, and a concentration between 0.5 and 1.5 mM produced distorted prisms (corners grew more than the middle of the faces). However, at concentrations greater than 1.5 mM, the corners grew much more than other parts of the crystal, giving them a star-shaped appearance. It has been suggested that star-shaped crystals should be produced when the growth of crystals is diffusion-controlled because the concentration of crystallizing solute shall be greatest at the corners. On the other hand, rectangular-shaped crystals can be envisaged when the concentration of depositing solute is the same over the entire surface. This takes place when the rate of consumption of the solute is slower than the rate of diffusion.

Crystals of anhydrous cholesterol obtained from ethanol under quiescent conditions with a low supersaturation value were platelike; those obtained from shaken solutions were elongated, and those precipitated from stirred solutions were needlelike. The same trend was observed when acetonitrile or methanol was used as crystallizing solvents.[8] Formation of needlelike crystals at high supersaturation of less polar solvent can be attributed to the significant solvent–solute interaction. Significant interaction probably results in preferential blocking of some faces, forcing the crystals to grow in one direction, resulting in a needlelike habit. Similarly, platy crystals are formed when the solute–solvent interaction is less.

Solute–solvent interaction is reported to influence the habit of stearic acid.[9] It is worth noting that the addition of small amounts of surfactants forces stearic acid crystals to grow only in one habit modification regardless of the nature of solvent and the crystallization conditions. This is because of the modification of solute–solvent interaction by added surfactant molecules. Therefore in the absence of significant solute–solvent interaction (using relatively inert solvents), the degree of supersaturation will perhaps predominantly govern crystal habit. Supersaturation also influences the particle size of crystallizing solute. At high supersaturation, nucleation is more rapid than growth. This results in the precipitation of fine particles. In thermal recrystallization, however, large crystals are produced because growth is faster than nucleation.[10]

The degree of saturation in diffusional boundary layer next to the predominant face of a growing crystal can alter crystal growth in unstirred systems. Such a stagnant boundary layer that may be as thick as 150 μM can restrict diffusion and deposition of crystallizing molecules on growing crystal faces. Adsorbed impurities/polymers shall further retard crystal growth.[11] Therefore the state of supersaturation of mother liquor appears to alter the shape of crystallizing particles by influencing the uniform deposition of molecules at different faces. It is important to note that the state of supersaturation depends not only on the choice of solvents used for solubilizing the drug, but also on the characteristics of the selected crystallizing solvent. The combined influence of both these solvents is critical in modifying habit as well as size of the crystallizing particles.

Rate of Cooling and Degree of Solution Agitation

Rate of cooling modifies crystal habit through its influence on the degree of supersaturation in mother liquor. Cooling a supersaturated solution of a drug or pouring it into crystallizing solvent maintained at low temperature immediately decreases the drug's solubility and results in rapid deposition of drug molecules on the nuclei.

Rapid cooling of a solution of naphthalene in ethanol or methanol produces thin plates, whereas slow cooling produces compact crystals. This is because of slow deposition of drug molecules on crystal faces at low rate of cooling.[12] It has been suggested that rapid cooling usually produces needle-shaped crystals because an elongated shape is most efficient in dissipating heat.[13] When the rate of cooling is decreased, the solution is maintained below saturation for longer duration. This results in delayed nuclei formation, slow deposition of crystallizing molecules, and, eventually, appearance of symmetric crystals. Slow cooling of a solution of acetazolamide in boiling water produced elongated prisms while faster cooling produced platy crystals.[14] Similarly, cooling an aqueous saturated solution of paracetamol from 65°C to 25°C produced polyhedral crystals. However, when concentrated solution in hot ethanol is added to water (3°C), platy crystals were obtained.[14] Hence modulation of the rate of cooling during crystallization could be employed as an effective means to alter crystal habit. As a corollary, habit changes shall be inevitable when a dosage form is repeatedly subjected to changes in temperature during processing or storage where the drug particles shall dissolve and then recrystallize to produce new crystals.

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The degree of solution agitation is logically expected to influence saturation level at solid–solvent interface of the nuclei as well as bring about temperature drop in the system. This is probably the reason for the formation of large platy crystals from quiescent solutions and elongated crystals from stirred solutions.[8] The effect of rate of solution agitation does not seem to have been studied extensively and needs critical evaluation.

Nature of Co-Solvent and Crystallizing Solvent

Crystallizing solvent is the medium into which a saturated drug solution prepared in a co-solvent is added to effect crystallization by precipitation. They may be a buffer (pH change method), water, or an organic solvent. As a prerequisite of this process of crystallization, the crystallizing solvent should be miscible with the liquid in which saturated solution of drug has been prepared. This requirement of miscibility implies that the intensity of solute–solvent interaction can be modified by selecting different co-solvents and/or crystallizing solvents.

Cholesterol is reported to crystallize as needles from ethanol and methanol and as platy crystals from acetonitrile.[8] Trimethoprim[16] and sulfamethoxazole[17] have been crystallized in distinctively different habits from different crystallizing solvents (Fig. 2). These studies also revealed that it was possible to obtain different habits of either drug belonging to the same polymorphic state using the same crystallizing solvent by just altering the process variables of crystallization such as co-solvent/crystallizing solvent ratio, temperature of co-solvent and crystallizing solvent, and rate of cooling. Co-solvents having high affinity for either drug required a higher ratio of co-solvent to crystallizing solvent for producing a well-defined morphology. A decrease in the initial supersaturation as a result of the elevated temperature of co-solvent or crystallizing solvent delayed the onset of nuclei formation and crystallization, thereby producing small crystals with equidimensional morphology. This was suggested to be a result of the slow and uniform deposition of solute molecules on the nuclei. However, variation of cooling rate did not appreciably affect the habit because of spontaneous precipitation of the drug. Therefore these studies suggest that process variables are as important as crystallizing solvent in modifying crystal habit and should be paid due attention while preparing crystals with specific attributes.

The interaction of a crystallizing solvent at various crystal–solution interfaces may lead to altered roundness of the growing crystal face/edges, change in crystal growth kinetics, and enhancement or inhibition of growth at certain crystal faces thus changing the habit.[18] In addition, polarity of the solvent and its preferential adsorption at selected crystal faces can significantly alter

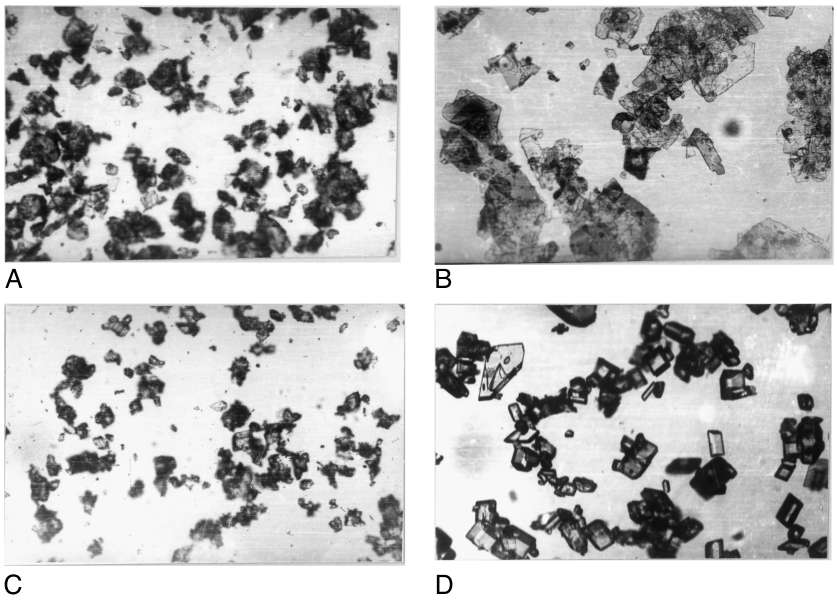

Fig. 2 Photomicrographs (magnification 200×) showing different habits of sulfamethoxazole (A and B same polymorph) and trimethoprim (C and D same polymorph): A and C—commercial drug samples; B—obtained by dissolving sulfamethoxazole in PEG 200 at room temperature and adding to water (70°C) in a ratio 1:20 followed by cooling at 4°C; D—obtained by dissolving trimethoprim in dimethyl formamide at room temperature and adding to water (70°C) in ratio 1:20 followed by cooling at room temperature.

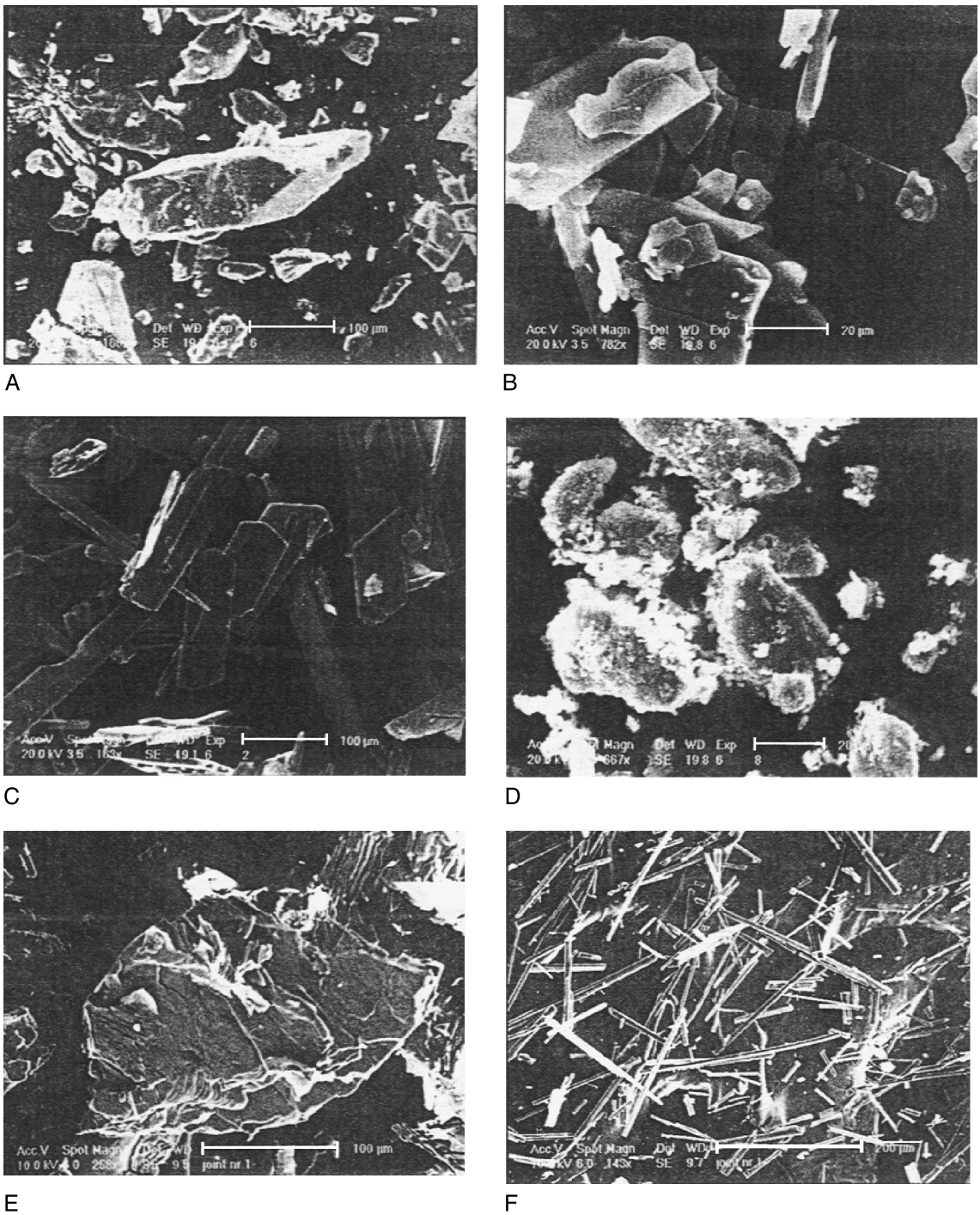

Fig. 3 SEM micrographs of commercial sodium diclofenac (anhydrous) (A); precipitated in tetrahydrate form (B); potassium diclofenac (dihydrate) (C); potassium diclofenac dihydrate (dehydrated at 100°C) (D); sodium diclofenac crystallized from methanol (E); potassium diclofenac crystallized from methanol (F). (From Ref. [20]. Reproduced with permission of John Wiley & Sons, Inc.)

the properties of crystallized solid particles. Nitrofurantoin has been reported to form a monohydrate when crystallized from formic acid/water (2:1) mixture because of the greater interaction of its polar regions with water than with formic acid. These water molecules have been suggested to be retained at the active sites during crystal growth, while desolvation of formic acid occurs more readily thereby producing an altered habit.[19]

Diclofenac sodium when dissolved in hot water and kept overnight crystallized in tetrahydrate form, whereas

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its potassium salt crystallized in dihydrate form. Fig. 3A shows that the commercial sodium diclofenac existed as sturdy opaque crystals. Thin leaflet-shaped crystals were obtained when it was precipitated from water (Fig. 3B). On the other hand, potassium salt was found to exhibit a regular bladed morphology (Fig. 3C) that was lost after dehydration at 100°C (Fig. 3D). Recrystallization of sodium and potassium diclofenac from methanol produced stratified (Fig. 3E) and thin elongated rod-shaped crystals (Fig. 3F), respectively.[20] Similarly, recrystallization of sulfadiazine from ammonia solution produced long, prismatic, smooth-edged crystals with markedly different physicotechnical properties.[21]

The nature of solvent has been found to have a profound effect on crystal habit of ibuprofen. Ibuprofen crystals precipitated from ethanol and acetone (solvents having high surface tension, dielectric constant, and less specific gravity) were thin, platy, and nearly circular-shaped, whereas those obtained from propylene glycol and 2-propanol were rod-shaped.[22] Similar observations have been reported by Garekani et al.[23] where all the habits of crystallized ibuprofen particles belonged to a common polymorphic state. Circular or polyhedral habits of ibuprofen obtained by precipitation from polar solvents can be ascribed to the insignificant interaction with these solvents. Significant interaction in sodium hydroxide (pH 10) solution resulted in the precipitation of needle-shaped crystals when the pH was decreased by the addition of hydrochloric acid. However, spherical agglomerates were obtained when ibuprofen was dissolved in acetonitrile because of its limited miscibility with water in which crystallization occurred on emulsion droplets (Fig. 4).[24]

It is important to note that unlike in precipitation method, both polar solvent, such as acetone, and nonpolar solvents, such as diethyl ether and hexane, produced needlelike crystals of ibuprofen when saturated solutions were cooled to 5°C over 120 min. Dichloromethane produced cubic, whereas acetonitrile produced spherical agglomerated crystals by this method. Solvent evaporation of ethanol gave platy crystals and diethyl ether gave needle-shaped crystals.[24] The ability of a solvent to crystallize ibuprofen into strikingly different habits without changing its polymorphic state can be suggested to be a result of the alteration of solvent–solute interaction brought about by the use of different crystallization methods. Ibuprofen dissolves to a greater extent in semipolar

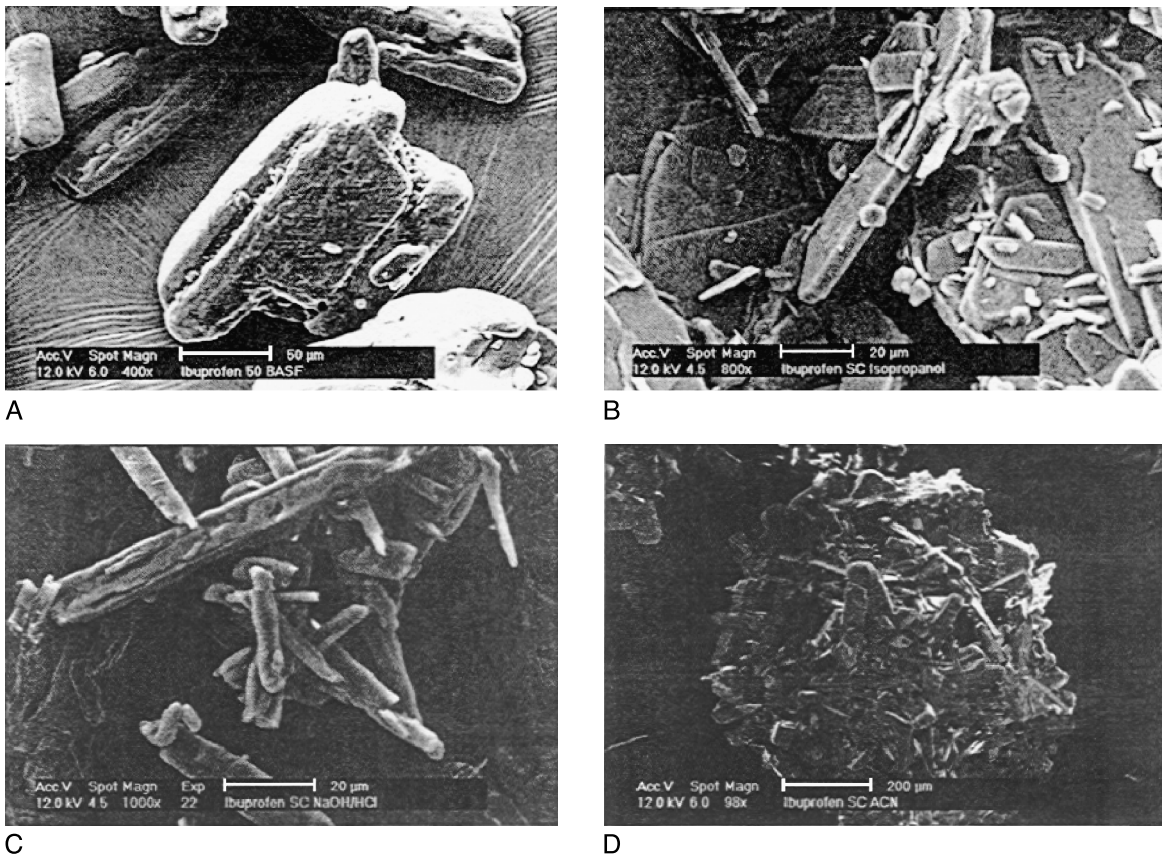

Fig. 4 SEM micrographs of ibuprofen commercial sample (A); crystals prepared by solvent change method using isopropyl alcohol (B); sodium hydroxide (C); acetonitrile (D). (From Ref. [24], p. 1083, by courtesy of Marcel Dekker, Inc.)

and nonpolar solvents, indicating a very high solute–solvent interaction. When crystallization is performed by precipitation in water, this strong interaction is weakened very soon and the crystal growth is not inhibited. This results in the deposition of solute molecules on all faces of the nuclei thus producing platy, polyhedral, or circular-shaped crystals. However, when crystallization is performed by temperature reduction or evaporation, the initially strong interaction is maintained till the end of the process. Therefore nuclei growth is inhibited on certain faces to the extent that both semipolar and nonpolar solvents produce needle-shaped crystals.

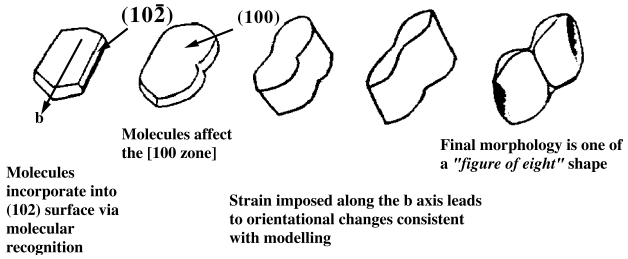

Fig. 5 Schematic illustration of growth process that produces dumbbell-shaped crystals of adipic acid. (From Ref. [36]. Reproduced with permission of John Wiley & Sons, Inc.)

Presence of Impurities

Ions, polymeric molecules, or other substances present in solute or solvent can act as impurities for the growing crystals. Surface adsorption of methylated spirit on mannitol seed crystals has been reported to produce highly porous surfaced crystals that were more resistant to vibrational segregation.[25] At the molecular level, impurities may get adsorbed in crystal lattice and disturb the regular and repeating arrangements of a crystal. Such defects give rise to local regions of molecular disorder relative to the original crystal structure and are said to be in an activated state because of the greater molecular mobility and exposure of more reactive chemical groups. Hence such defects in the crystals lead to enhanced reactivity, solubility, and dissolution. Detailed discussion on such crystal lattice defects that lead to alteration in polymorphic state is not within the scope of this topic. However, because of their importance in influencing stability, dissolution, solubility,[26,27] and thereby biological performance, it is necessary to ensure the absence of polymorphic modifications as a result of the crystal lattice defects to clearly define the role of crystal habit.

It will be more pertinent here to understand the mechanisms by which lattice defects created by added impurities modify crystal habit. Whetstone[28–30] suggested that habit modification of inorganic salts depended on the anionic and cationic substitution and on the nature of substitution present in dyes. At low saturation level, an increase in the impurity concentration (cationic or anionic surfactants) was found to result in cessation of growth at certain crystal faces, whereas at high saturation, these surfactants produced less effect on the habit of adipic acid. Furthermore, anionic and cationic surfactants as impurities were found to modify the habit to needles and flakes, respectively.[31,32] When valeric or undecanoic acid were added as impurities, adipic acid crystallized as cigar-shaped spars with rounded edges. Further increase in the concentration of impurities produced fused pairs of spherules. A linear plot of the maximum growth rate slope of desupersaturation of adipic acid against concentration of caproic acid (impurity) suggested that its selective adsorption on various faces except near the surface was responsible for habit modification of adipic acid.[33] Earlier, dumbbell-shaped appearance of modified crystals of adipic acid was suggested to arise from crystallographic twinning because of the similarity of the *a*- and *c*-axes of the unit cell.[34] These crystals have been reported to possess modified density, crystal energy, and dissolution rate.[35] Recently, it has been found that decanoic acid gets incorporated into adipic acid crystal {102} surface that results in loss of facets in the {010} zone. These lattice distortions result in crystals having misaligned domains, but they are not crystallographically twinned.[36] Fig. 5 summarizes the steps that lead to the final dumbbell or ''figure-of-eight'' shaped morphology of adipic acid.

Apart from dyes and surfactants, polymeric molecules also influence the crystal habit of developing crystals. Sulfathiazole has been reported to grow out in finger-like protrusions in the presence of polyvinylpyrrolidone (PVP). It was suggested that PVP formed a ''net'' over the developing crystals. The effective pore size in the ''net'' and growth inhibition depended on the relative transport rates of PVP and sulfathiazole to crystal surface.[37] Carbamazepine (anhydrous) is known to convert to the dihydrate form in water,[38] and the growth of these crystals occurs by whisker mechanism. Both hydroxypropylmethyl cellulose (HPMC) and egg albumin (EA) have been found to retard the conversion of anhydrous carbamazepine to the dihydrate form in a concentration-dependent manner. In addition, HPMC was found to prevent the crystallization of the $\propto$-form. These preventive effects of HPMC at low concentrations could not be explained by simple adsorption because the polymer chain remained entangled and less mobile to enwrap all growing sites effectively. Therefore it was proposed that HPMC served as a template for heterogeneous nucleation, to which carbamazepine dimer attached through hydrogen bonding. More specifically, structural matching between interatomic distances

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in the crystal lattice and intra-atomic distances along the polymer chain can be envisaged to be responsible for transformation inhibition.[39] On the other hand, with EA, the prevention of crystallization of ∝-form was found to be less pronounced because of its lower ability to form hydrogen bonds with carbamazepine molecules. Egg albumin was found to decrease the degree of carbamazepine conversion to dihydrate form and whisker growth through an increase in aggregation of its dihydrate crystals. An increase in contact angle after addition of EA and reversibility of EA effect on aggregation by sodium dodecyl sulfate suggested that EA prevented the crystal growth of carbamazepine by increasing the dihydrate–liquid interfacial tension. Additionally, EA served as a microsubstitute for nucleation, thereby enhancing the two-dimensional nucleation on whisker sides.[40]

It is interesting to note that PVP that contained only one hydrogen bonding carbonyl group per monomer unit was ineffective even at 500 times higher molar concentration than the minimum concentration of HPMC required to completely inhibit the transformation of carbamazepine to its dihydrate from.[40] In contrast, crystal habit of paracetamol was found to be effectively modified by PVP with higher influence being exerted by higher molecular weight derivatives (PVP 10 000 or 50 000). Adsorption of high molecular weight PVP onto paracetamol growing crystals resulted in nearly spherical structure consisting of numerous rod-shaped microcrystals agglomerated together without any change in polymorphic state.[41]

Discrepancies regarding the influence of polymeric impurities on habit modification seem to be because of the complex nature of nuclei formation and growth during crystallization. Polymers can get incorporated into the crystal only when they are similar to the crystallizing molecule in size or structure, which is often not the case. Hydroxypropylmethyl cellulose has been found to act as both growth inhibitor and habit modifier of hydrocortisone acetate, whereas PVP and polyethylene glycol 400 acted predominantly as growth inhibitors. This was suggested to be a result of the stronger interaction of HPMC (via hydroxyl groups) at the surface of the growing crystal. The influence becomes more pronounced in unstirred systems where a diffusional boundary layer adjacent to the growing crystal surface is formed. The accumulation of polymer molecules in this layer provides resistance for drug molecules to diffuse through and leads to growth inhibition. Additionally, habit gets modified when the polymeric groups get preferentially adsorbed at particular crystal faces thereby preventing growth of these faces, while other faces grow normally. Polymers that do not interact and get just adsorbed therefore lack the ability to modify the habit.[11]

Polymorphic molecules such as methacrylic co-polymers may modify crystal habit by virtue of their ability to form micelles because of the presence of quaternary ammonium groups in their molecules. Water-insoluble eudragits (RS and RL) that increased the solubility of ibuprofen produced more reduction in crystal yield than the water-soluble eudragits (L and S). However, all these polymers produced agglomerated spherical crystals with rough surfaces that were exhibited increased porosity. Greater pore diameter in crystals precipitated in the presence of eudragits accompanied with increased intraparticle porosity suggested the absence of polymer deposition in the empty spaces between microcrystals in the agglomerates.[42]

Tailor-made impurities can be used for specific drug molecules. The use of *p*-acetoxyacetanilide (PAA) during crystallization of paracetamol has been found to produce columnar crystals. The incorporation of PAA into critical nucleus delayed the onset of nucleation and resulted in crystals that exhibited significant mosaic spread, implying the development of significant strain/defect content in the crystals.[43]

Therefore irrespective of the mechanism under operation, the addition of impurities during crystallization can be advantageously employed to engineer crystal habit if the impurity is known to modify the growing crystal into a morphology that is desirable from the viewpoint of dosage form design and performance.

SIGNIFICANCE OF CRYSTAL HABIT IN DOSAGE FORM PERFORMANCE

Tablet Formulation

It is well known that crystal habits exhibiting symmetric morphological characteristics such as the cubic system present no difficulty during direct compression into tablets. Jaffe and Foss[44] pointed out that binary compounds are found predominantly in the cubic and hexagonal system and are characterized by higher symmetry than ternary and more complex compounds found in the rhombic, monoclinic, and triclinic systems. Low-symmetry structures such as carbonates of calcium, lead, nickel, potassium, silver, and sodium have been reported not to form tablets on direct compression. The regular spherical particles of spray-dried lactose form stronger tablets compared with angular particles on direct compression.[45] Similarly, replacement of platy habit (form B) by nonplaty (form A) crystals of tolbutamide has been reported to obliterate capping of tablets.[46] These findings suggest symmetricity of crystals to be a prerequisite for direct compression.

Successful tableting requires uniform flow from the hopper, proper packing, rearrangement, reduction in porosity, and deformation of particles in the die cavity. Flat

needle-shaped crystals of aspirin have been found to align themselves parallel to the punch face, forming a layered structure that exhibited low lateral stress transmission characteristics.[47] An increased radially transmitted stress with flaky powered material[48] reinforces this contention. Apart from the mechanical influence of crystal shape, another dominant factor that results from the anisotropy of cohesion and hardness (of low-symmetry crystals) also contributes to the ease of compression. As crystal habit varies, the dominant faces vary in relation to this anisotropy and tend to orient the crystals during compaction process thus exhibiting great differences in packing and compression kinetics.

Cubic sodium chloride crystals that pack in a bricklike fashion have been found to exhibit greater density than the dendritic crystals. In addition, reduced slip between dendritic crystals made rearrangement difficult and resulted in greater loss of compaction force to the die wall.[49] Ibuprofen is generally crystallized industrially from hexane in the form of elongated needlelike crystals. This shape has been found to be unsuitable for tableting because of the poor flow properties. Equidimensional crystals obtained using methanol have been reported to possess better compaction features and flow properties.[23,50] Crystal morphology of excipients such as powdered cellulose[51] and calcium alumina trihydrate[52] has also been reported to significantly influence strength, content uniformity, and disintegration time of tablets.

The platelike nitrofurantoin crystals are reported to undergo greater densification and plastic deformation than the needlelike crystals. Furthermore, tablets prepared from needlelike crystals exhibited a higher degree of axial recovery after ejection. This was suggested to be a result of the development of larger nonpolar faces in platelike crystals that were crystallized from formic acid than polar faces of needlelike crystals crystallized from formic acid/water mixture. The relative abundance of these faces probably affected the magnitude and the strength of bonding during compression.[53]

An orthorhombic structure is characterized by high molecular density and weak interplane bonds. During the initial stages of compression cycle, these planes have been suggested to act as slide planes giving rise to substantial interparticle rearrangement, thus resulting in volume reduction. At high pressures, these crystals undergo plastic deformation with low elastic recovery as compared with monoclinic form, thus increasing the points of contact in the compact. Because of these reasons, orthorhombic paracetamol crystals exhibited good tablet forming property with no tendency of capping.[54] Platy crystals of paracetamol have been reported to exhibit lower correlation coefficient values for Heckel plots and strain rate sensitivity, indicating greater fragmentation compared with polyhedral crystals. Tablets compressed from platy crystals showed higher elastic recovery, suggesting that these crystals underwent less plastic deformation.[15] It has been suggested on the basis of molecular geometry of paracetamol crystal lattice that the cleavage along the {010} plane follows a serrated path and the interplanar bonding is of van der Waals type. However, along both {110} and {210} planes, cleavage requires breakage of two hydrogen bonds per unit cell. In addition, the lowest attachment energy and maximum slice energy for the {010} plane strongly suggested that the fracture in paracetamol crystals occurred along the {010} crystal plane.[55,56]

Compression of particles may alter the internal structure as well as their morphology. These changes are opposed by intermolecular forces that restore the crystal to its original form and results in elastic recovery. If the intermolecular forces are exceeded, then plastic flow occurs. It has been suggested for aspirin that the displacement occurring along the slip planes inside the crystal moved in an orderly manner to a new location, with the molecular packing arrangement remaining unchanged. However, cubic sodium chloride crystals possess numerous potential slip planes for plastic deformation, and microscopic examination did not reveal shearing effects. This indicates that shearing occurred at the molecular level in cubic sodium chloride crystals.[57] An increase in compression pressure decreased the crystallinity of lactose, producing stronger tablets as a result of the more activated crystals dissipating acquired energy by interparticle bonding.[58] Compacts made from equidimensional crystals of L-lysine monohydrochloride dihydrate in the absence of excessive pressure showed wider flaws (wider cracks between particles), whereas those from long rod-shaped crystals had longer flaws. These compacts of rod-shaped crystals were found to have poor strength probably because of the higher stress intensity at the crack tip that propagated to longer distances along the interparticle boundary.[59] In addition, variation in the degree of surface crystallinity has been found to exhibit enormous influence on tablet properties.[60] Hence an equidimensional habit that undergoes the highest degree of densification and exhibits a tendency to form new bonds at the fragmentation sites during compaction seems to offer great advantage for tablet formulation.

Dissolution

Dissolution of a drug depends on the physicochemical and physicotechnical properties of drug particles. These crystal attributes directly affect the absorption kinetics of a drug and thereby bioavailability of dosage forms. This assumes greater importance for drugs exhibiting low solubility that makes absorption to be dissolution rate-limited. It is established that an increase in solubility can be brought by modifying the polymorphic state of a

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compound. But the influence on other attributes such as stability, biological efficacy, metabolism, etc. as a result of change in polymorphic state demands a thorough investigation while using this approach. Modifying surface morphology of crystals without altering the polymorphic state seems to offer an attractive alternative approach for enhancing the dissolution of drugs. Furthermore, it is necessary to standardize the surface characteristics for minimizing differences in dissolution behavior of drug particles obtained from different batches/sources.

The size and the number of crystal faces exposed to solvent attack determine the amount of drug dissolved. It was shown that the lifetime of potassium ferricyanide crystal was proportional to the smallest length of the crystal face in contact with liquid paraffin–water interface. Furthermore, nonisometric dissolution of the crystal face indicated a change in crystal shape during dissolution.[61] The shape factor of a single crystal of potassium dichromate changed significantly after 50% dissolution and was dependent on the degree of nonisometricity of the crystal.[62] These reports indicate that a continuously changing dissolution profile can be anticipated for certain habits such as rods and needles because of the more solvent attack on predominant faces of the crystals as dissolution progresses.

At the molecular level, dissolution can be visualized to involve interaction of solvent with functional groups in the drug particles. Additives/impurities present in drug particles may alter the intensity of drug-dissolution medium interaction thereby modifying dissolution characteristics. Hydroxypropyl β-cyclodextrin has been found to be more effective than PVP in inhibiting the crystal growth and enhancing the dissolution of nifedipine.[63] However, additives may sometimes even reduce the dissolution rate. A combination of Eudragit RS and cellulose acetate phthalate has been shown to alter the habit and sustain the release of an iron chelator.[64] Crystallization of sulfadiazine from ammonia solution significantly decreased the dissolution rate because of the reduced wettability of the outer surface of recrystallized particles that seems to arise from the influence of crystallizing liquid.[21] Depending on the solvent used for crystallization, internalization of the functional groups that are less attracted to the liquid takes place. Similarly, reduced wettability associated with agglomeration of crystals has been proposed to decrease the dissolution of ibuprofen crystals recrystallized from acetonitrile or methanol.[24] It is important to note that nonionic impurities such as Tween 80 that do not disturb the arrangement of sulfadiazine molecules in ammonia solution did not appreciably affect the dissolution of recrystallized sulfadiazine. On the other hand, although the addition of sodium chloride as an impurity did not increase wettability, the dissolution of crystals was enhanced. It has been proposed that probably sodium chloride, as a result of its ionic nature, reduced the interaction of ammonia with sulfadiazine through ion–dipole interaction. This in turn resulted in reducing the effect of ammonia on orientation of functional groups present in sulfadiazine molecules during recrystallization, thereby negating the dissolution retarding influence of ammonia on recrystallized sulfadiazine crystals.[21]

The literature abounds with reports of investigations on enhancement of dissolution of drugs having low aqueous solubility by change in crystal habit. Ibuprofen crystals prepared by precipitation from ethanol and acetone have been reported to exhibit enhanced dissolution than the rod-like crystals obtained from propylene glycol and 2-propanol.[22] Preparation of ibuprofen crystals by using phase partition technique and employing Tween 80 in the binding solvent have been found to produce microcrystals which when compressed into tablets exhibited dissolution comparable to that of commercial product with respect to USP 24 requirement (Q > or = 80 % at 60 min).[65] Other drugs that are known to have low aqueous solubility such as aspirin,[66] mefenamic acid,[67] and etoposide[68] have also been reported to exhibit better dissolution after modification of crystal habit. However, results of dissolution enhancement should be cautiously interpreted because most studies do not often aim at delineating the role of crystal habit from that of polymorphic state which usually accompanies recrystallization of drug particles.

A pharmaceutical sample usually contains a mixture of habits. This is because of the complex natures of crystallization process in which even a scratch in the container or presence of dust particles is capable of initiating nuclei formation and modifying habit of growing crystals. Because of these mixed habits, the dissolution profile cannot be ascribed to a particular habit unless this shape constitutes a significant proportion of the bulk. Hence to correctly characterize the dissolution behavior and evaluate the contribution of various crystal faces, studies are made on single crystals. Prasad et al.[69] have reported that the dissolution rate of {001} and {110} faces of paracetamol crystals grown in the presence of molecularly similar additive *p*-acetoxyacetanilide were higher than that of pure paracetamol. This was attributed to the distribution of strain in the crystal that increased its solubility.[69] Apart from inclusion of impurities, processing variations can also lead to development of such strains. Moisture taken up even in low amounts in these areas of ''strain'' or ''disorder'' can plasticize the solid and promote molecular mobility that results in enhanced dissolution, chemical degradation, and solid-state changes such as recrystallization.[26,27]

It is noteworthy that modified habits of trimethoprim and sulfamethoxazole having different habits but

belonging to the same sieve fraction and polymorphic state exhibited significantly different dissolution profiles. For both drugs, symmetric crystals were found to dissolve faster probably because of the uniform exposure of all the surfaces to dissolution medium. However, symmetric crystals having a higher size factor (length × breadth) exhibited slow dissolution during the early phase. But during the later phase, as the size factor decreased, the dissolution rate of these crystals was found to increase. Symmetrical crystals that possessed low zeta potential exhibited considerable aggregation and dissolved slowly.[16,17] It is perhaps for the first time that change in crystal habit has been shown to be associated with alteration of surface charge. The fact that surface charge has an ability to influence not just the aggregation state but also other powder characteristics such as mixing, flowability, dissolution, and solubility, it seems logical to evaluate the electrophoretic motility of recrystallized particles. Nevertheless, altering crystal habit seems to offer an approach for modifying the dissolution behavior of drugs.

Suspensions

The influence of crystal habit on performance of suspension dosage form can be envisaged to be more pronounced than other dosage forms because of greater space available for reorientation and packing of dispersed particles. Furthermore, selection of a stable habit is essential to avoid crystal growth that leads to physical instability during the shelf life of suspensions.

Investigations on trimethoprim[16] and sulfamethoxazole[17] suspensions have revealed that crystals with high shape factor ($1/L \times 1/B$) exhibited high sedimentation volume and could be easily redispersed. It was suggested that during settling, these crystals perhaps formed an end-to-face rather than an end-to-end framework because this would result in decreased free energy of the system. Although these anisometric crystals possessed high zeta potential, they tend to induce ''self-flocculation,'' which produced a scaffold-like, porous pack structure that was less susceptible to overhead pressure of settling particles. On the other hand, crystals with irregular shape exhibited low sedimentation volume and were not easily redispersed because of cake formation. This was because of the reorientation of irregular crystals during sedimentation that lead to close-fit packing. It is noteworthy that a massive increase in sedimentation volume (sixfold) was obtained by employing rod-shaped crystals of trimethoprim in deflocculated suspension.[16] The pharmacokinetics of both trimethoprim and sulfamethoxazole crystals was not significantly altered as compared with the respective pure drug powders probably because of their reported rapid absorption which does not render their bioavailability to be dependent on dissolution. However, studies on drugs that have inherently low solubility and/or low intestinal permeability are advocated to test the validity of this hypothesis.

It is important to consider the influence of interaction between functional groups of drugs that leads to their habit modification when formulated in suspension dosage form. Proton transfer from the N atom of sulfamethoxazole

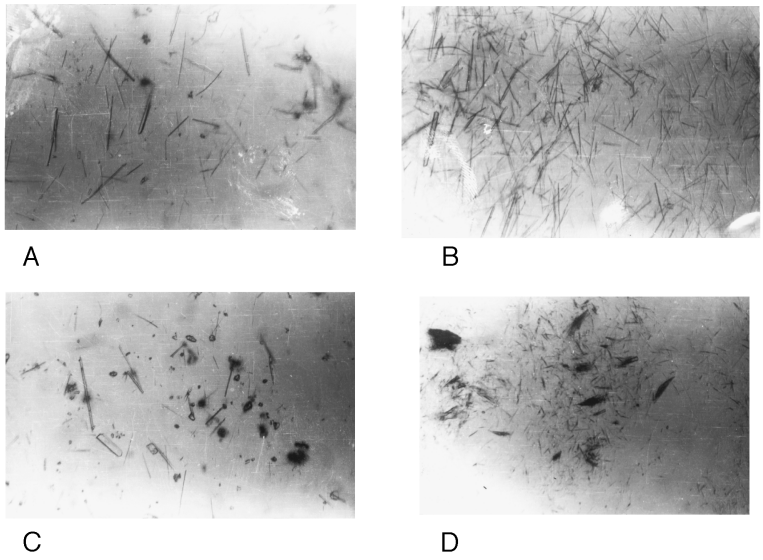

Fig. 6 Photomicrographs (magnification 200×) of crystals showing modified habit produced after interaction between aqueous dispersions of sulfamethoxazole and trimethoprim: molar ratio 5.73:1 (A); molar ratio 1:1 (B); HPMC added before mixing aqueous dispersions (C); HPMC added after mixing aqueous dispersions (D).

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to the pyrimidine basic N1 atom of trimethoprim has been reported to occur in their equimolar complexes.[70] Bettinetti et al.[71] have reported nucleation of the complex of trimethoprim and sulfamethoxypyridazine (1:1) to be accelerated by water or wet granulation. Our studies on cotrimoxazole (unpublished results) revealed immediate formation of fine needle-shaped crystals irrespective of the initial shape of sulfamethoxazole and trimethoprim crystals as a result of the interaction between the two drugs in suspension form. Small needles (Fig. 6A) were produced when the aqueous dispersions of both drugs were mixed in amounts that are normally present in pharmaceutical suspensions (molar ratio sulfamethoxazole/trimethoprim: 5.73:1). Using the same processing conditions, long needle-shaped crystals were produced when the molar ratio was 3:2, 1:1, 2:3, or 1:2 (Fig. 6B), and these dispersions exhibited a sedimentation volume of 1.00 after storage over 2 months at 35°C. Furthermore, addition of aluminum chloride as flocculating agent modified the original crystals to long needle-shaped crystals. This was also evident when aluminum chloride was added to aqueous dispersion of trimethoprim. Addition of HMPC (1% w/v) before mixing dispersions of both drugs did not allow complete interaction as a result of which formation of needle-shaped crystals was found to be incomplete (Fig. 6C) and the resultant dispersions exhibited caking after storage. Perfect needles were formed but possessed shorter length (Fig. 6D) when HPMC was added after mixing the dispersions of both drugs. The results of these investigations strongly indicated that habit modification can result from interaction between functional groups in physical mixtures of drugs and that the intensity of modification can be altered by the formulation and processing variables. This influences the stability of suspension dosage forms, and hence occurrence of such habit modifications should be given due attention during preformulation. As a corollary, this approach could be used to enhance the physical stability of drug suspensions that are prone to caking on storage. This can be achieved by employing interaction between the drug and an inert substance to produce crystals with appropriate habit that can form a porous pack structure that will embed the drug particles. Such suspensions shall exhibit high sedimentation volume and ease of redispersibility. However, feasibility of using this approach is yet to be tested.

CONCLUSION

Crystal morphology is an important attribute of solids. Both crystal shape (habit) and surface appearance can be significantly altered by the process variables of crystallization. Crystallization, which is often used for purifying/recrystallizing a drug powder, may modify either polymorphic state, crystal habit, or both. Although seemingly trivial, crystal habit plays a significant role in influencing packing, flowability, compressibility, dissolution, and sedimentation characteristics of pharmaceutical powders. Therefore selecting a stable polymorph may not alone solve the problem if the polymorph exists in distinctly different habits that can modify the physical stability of the dosage form. In addition, polymorphic transformations or crystal growth during storage may accompany change in crystal habit. Furthermore, development of strain in crystal lattice either because of impurities/additives or during processing can lead to changes in habit that can alter the performance of dosage form. Hence it is imperative to study changes in crystal habit along with changes in polymorphic state at critical processing stages. This shall help in maintaining uniformity in raw material characteristics and batch-to-batch dosage form performance besides formulating a stable dosage form with required performance.

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